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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of Schwartz, et al.

Serial No. 10/695,509 Examiner: Fetterolf, Brandon J.

Filed: October 28, 2003 Art Unit: 1642

For: METHODS FOR PREVENTION AND TREATMENT OF CANCER

DECLARATION UNDER 37 CFR 1.132

I, Gary G. Schwartz, Ph.D., M.P.H, Ph.D., the undersigned, am a citizen and resident of the United States, and hereby declare the following:

WHEREAS, I received a B.A degree in psychology from Pomona College in Claremont, California (1978); a Ph.D. in Biological Psychology from the State University of New York Downstate Medical Center in 1985 and, at the University of North Carolina at Chapel Hill, received a Master's in Public health in 1988, completed a Postdoctoral Fellowship in Cancer Epidemiology in 1989, and received a Ph.D in epidemiology in 1993; and

WHEREAS, I have authored or co-authored more than 50 peer-reviewed research papers published in scientific journals and multiple abstracts, book chapters, and presentations in my field of expertise (a representative list of which is attached hereto as Appendix A); and

WHEREAS, I currently hold the joint positions of:

- Associate Professor (tenured), Department of Cancer Biology, Wake Forest University School of Medicine, Winston-Salem, NC; and

- Associate Professor, Department of Epidemiology & Prevention, Wake Forest University School of Medicine; and

- Scientific Director, Prostate Cancer Center of Excellence, Comprehensive Cancer Center of Wake Forest University, Winston-Salem, NC.

WHEREAS, I previously held the positions of:

- Associate Professor, Department of Epidemiology & Public Health, University of Miami School of Medicine, Miami FL (June 1997-June 1999);

- Research Associate Professor, Department of Epidemiology & Public Health, University of Miami School of Medicine, Miami FL (August 1994-May 1997);

- Assistant Professor, Department of Clinical Epidemiology and Preventive Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA (May 1991-July 1994); and

WHEREAS, I am a named inventor on the subject patent application, and have read and reviewed the subject patent application, as filed and amended, as well as the instant Office Action and the references cited therein.

NOW THEREFORE, BEING established as an expert in the field of cancer research relating to the subject matter of the claimed invention, I make the following statements and render my opinion based on my knowledge of the inventions and in view of my experience and expertise:

THAT, the scientific literature available at the time the invention was made established that, although it was known that prostate cancer cells possess receptors for $1,25(OH)_2$ vitamin D (vitamin D receptors or VDR) and that $1,25(OH)_2$ vitamin D at pharmacologic levels could inhibit the growth of these cells (Peehl D, et al. Antiproliferative effects of 1,25-Dihydroxyvitamin D_3 on primary cultures of human prostatic cancer cells. *Cancer Res* 1994;54:805-810), there was no known mechanism nor reason to believe that the prohormone, 25-hydroxyvitamin D, as claimed, would be effective in inhibiting the growth of prostate cancer cells, except at pharmacologic (potentially toxic) doses. This is because 25-OH vitamin D is known to have 1/500th to 1/1000th the affinity of $1,25(OH)_2$vitamin D for the receptor for $1,25(OH)_2$ vitamin D. The concentration of 25-OH vitamin D needed to mimic pharmacologic effects of $1,25(OH)_2$vitamin D could be potentially toxic.

Our demonstration, for the first time, that prostatic cells possess vitamin D-1α-hydroxylase and convert 25-Hydroxyvitamin D into $1,25(OH)_2$ vitamin D, *intracellularly*, avoids the need to administer $1,25(OH)_2$ vitamin D systemically (and thus reduces the

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risk of hypercalcemia associated with systemic administration of 1,25(OH)$_2$ vitamin D). It also means that 25-OH vitamin D need not be given at potentially toxic doses since the 25-OH vitamin D will be converted to 1,25(OH)$_2$ vitamin D intracellularly by cells that possess vitamin D-1α-hydroyxlase. There is no prior art showing that prostate cells possess vitamin D-1α-hydroyxlase and can convert 25-Hydroxyvitamin D into 1,25-Dihydroxyvitamin D.

Second, an inhibitory role for 1,25(OH)$_2$ vitamin D could not reasonably have been predicted based solely on the knowledge that cells, such as prostate cancer cells, possess vitamin D receptors (VDRs). This is because the effects of 1,25(OH)$_2$ vitamin D are not uniform. The 1,25(OH)$_2$ vitamin D may have no effect on cell growth and may even stimulate it. For example, cancer cells which fail to respond to the antiproliferative effects of 1,25(OH)$_2$ vitamin D despite the presence of functional VDR are well-described in the literature (Buras R. et al., Vitamin D receptors in breast cancer cells. *Breast Cancer Res Treat* 1994; 31:191-202; Narvaez CJ, et al., Characterization of a vitamin D3-resistant MCF-7 cell line. *Endocrinology* 1996;137:400-409). Moreover, although vascular cells possess VDR, exposure to 1,25(OH)$_2$ vitamin D in these cells is a potent growth stimulator (Koh, E. et al. 1,25-Dihydroxyvitamin D$_3$ binds specifically to rat vascular smooth muscle cells and stimulates their proliferation in vitro. *Life Sciences* 1988;42: 215-233; Mitsuhashi T, et al. 1,25-Dihydroxyvitamin D$_3$ modulates growth of vascular smooth muscle cells. *Journal of Clinical Investigation* 1991; 87: 1889-1895.) These examples were published in 1988 through 1996 and thus were part of the literature at the time the present invention was made. Thus, knowledge that cells possess VDR is not a reliable predictor that they would respond to 1,25(OH)$_2$ vitamin D by a reduction in proliferation.

THEREFORE, it is my expert opinion that there would not have been "a reasonable expectation of success that by administering 25-hydroxyvitamin D, one would achieve a safe and effective alternative to 1,25-D3, e.g., calcitiol, for the treatment of cancer" as stated in the Office Action dated April 10, 2008 for the subject application.

I HEREBY DECLARE THAT ALL STATEMENTS MADE HEREIN OF MY OWN KNOWLEDGE ARE TRUE AND THAT ALL STATEMENT MADE ON INFORMATION AND BELIEF ARE BELIEVED TO BE TRUE; AND FURTHER THAT THESE STATEMENTS WERE MADE WITH THE KNOWLEDGE THAT

WILLFUL FALSE STATEMENTS AND THE LIKE SO MADE ARE PUNISHABLE BY FINE OR IMPRISONMENT, OR BOTH, UNDER 18 U.S.C. 1001 AND THAT SUCH WILLFUL FALSE STATEMENTS MAY JEOPARDIZE THE VALIDITY OF THE PATENT APPLICATION OR ANY PATENT ISSUED THEREON.

Further, Declarant sayeth naught.

Date: August 11 2008 By: Gary G. Schwartz, Ph.D., M.P.H, Ph.D.

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APPENDIX A

PUBLICATIONS AUTHORED OR CO-AUTHORED BY GARY G. SCHWARTZ, PhD, MPH, PhD

Refereed Journal Articles

1. Cohen SW, Sherman M, **Schwartz GG**, Banko W, Cohen H, Mahl C. Lacrimal outflow patency demonstrated by chemiluminescence. Archives of Opthalmology. 1980;98:127-128.

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3. **Schwartz GG**, Rosenblum LA. Allometry of primate hair density and the evolution of human hairlessness. American Journal of Physical Anthropology 1981;55:9-12.

4. **Schwartz GG**, Hulka BS. Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis) Anticancer Research 1990;10:1307-1311.

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15. **Schwartz GG**, Whitlach LW, Chen TC, Lokeshwar B, Holick MF. Human prostate cells synthesize 1,25-Dihydroxyvitamin D_3 from 25-Hydroxyvitamin D_3. Cancer Epidemiology, Biomarkers, and Prevention 1998;7:391-395.

16. Lokeshwar BL, **Schwartz GG**, Selzer MG, Burnstein KL, Zhuang S-H, Block NL, Binderup L. Inhibition of prostate cancer metastasis in vivo: A comparison of 1,25-Dihydroxyvitamin D (calcitriol) and EB1089. Cancer Epidemiology, Biomarkers & Prevention, 1999;8:241-248.

17. John EM, **Schwartz GG**, Dreon DM, Koo, J. Vitamin D and breast cancer risk: The NHANES I Epidemiologic Follow-up Study, 1971-1975 to 1992. Cancer Epidemiology, Biomarkers & Prevention 1999;8:399-406.

18. Barreto A, **Schwartz GG**, Woodruff R, Cramer SD. 25-Hydroxyvitamin D_3, the prohormonal form of 1,25-Dihydroxyvitamin D_3, inhibits the proliferation of primary prostatic epithelial cells. Cancer Epidemiology, Biomarkers & Prevention 2000;9:265-270.

19. Chen TC, **Schwartz GG**, Burnstein KL, Lokeshwar BL, Holick MF. The use of 25-Hydroxyvitamin D_3 and 19-nor-1,25-Dihydroxyvitamin D_2 as therapeutic agents for prostate cancer. Clinical Cancer Research 2000:6:901-908.

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28. **Schwartz GG**, Eads D, Rao A, Cramer SD, Willingham MC, Chen TC, Jamieson DP, Wang L, Burnstein KL, Holick MF, Koumenis C. Pancreatic cancer cells express 25-Hydroxyvitamin D-1-α-Hydroxylase and their proliferation is inhibited by the prohormone 25-Hydroxyvitamin D$_3$. Carcinogenesis 2004, 25: 1015-1026.

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50. **Schwartz GG.** Prostate cancer, serum Parathyroid Hormone and the progression of skeletal metastases. Cancer Epidemiology Biomarkers & Prevention, 2008, 17: 478-83.

51. **Schwartz GG**, Eads D, Naczki C, Northrup S, Chen TC, Koumenis C 19-nor-1α,25-Dihydroxyvitamin D_2 (Paricalcitol) inhibits the proliferation of human pancreatic cancer cells *in vitro* and *in vivo*. Cancer Biology & Therapy, 2008, 7: 430-436.

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Book Chapters

1. **Schwartz GG**, Rosenblum LA. Primate infancy: Problems and developmental strategies. In: Wolman B (Ed), Handbook of Developmental Psychology, Englewood Cliffs: Prentice-Hall, 1982, pp. 63-75.

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